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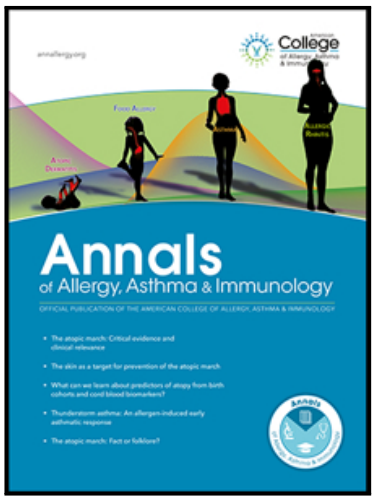

Asthma and COVID-19 related outcomes in hospitalized patients: A single center experience

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Title: Asthma and COVID-19 related outcomes in hospitalized patients: A single center experience

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Author Contributions:

Drs. Njira Lugogo and Amy Ludwig conceived the study, and along with Drs. Christopher Fung, Dr. Shijing Jia, Michael Sjoding, and Jonathan Troost participated in study design. Drs. Fung and Sjoding provided patient databases, and Dr. Troost performed the statistical analysis. Drs. Laura Leuenberger, Catie Tarantine, Ella Cristoph, and Rayan Kaakati abstracted patient data from the electronic medical record. Drs. Ludwig, Lugogo, and Caryn Brehm drafted the manuscript. All authors read and approved the final manuscript.

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Keywords:

Abbreviations/Acronyms:

ACE2	Angiotensin-converting enzyme 2
AEC	Absolute eosinophil count
ALC	Absolute lymphocyte count
CAD	Coronary artery disease
CCI	Charlson comorbidity index

CDC	Centers for Disease Control and Prevention
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
FEV1	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IRR	Incidence rate ratio
LABA	Long-acting beta agonist
LAMA	Long-acting anti muscarinic
LTRA	Leukotriene receptor antagonists
OCS	Oral corticosteroids
OSA	Obstructive sleep apnea
PFT	Pulmonary function tests
US	United States

Abstract

Introduction

Several chronic conditions have been associated with a higher risk of severe coronavirus disease 2019 (COVID-19), including asthma. However, there are conflicting conclusions regarding risk of severe disease in this population.

Objective

We seek to understand the impact of asthma on COVID-19 outcomes in a cohort of hospitalized patients and if there is any association between asthma severity and worse outcomes.

Methods

We identified hospitalized COVID-19 patients with confirmatory PCR testing with (n=183) and without asthma (n=1319) using ICD-10 codes between March 1 – December 30, 2020. We determined asthma maintenance medications, pulmonary function tests (PFTs), highest historical absolute eosinophil count and IgE. Primary outcomes included death, mechanical ventilation, ICU admission, ICU and hospital length of stay (LOS). Analysis were adjusted for demographics, comorbidities, smoking status, and timing of illness in the pandemic.

Results

In unadjusted analyses, we found no difference in our primary outcomes between asthma and non-asthma patients. However in adjusted analyses, asthma patients were more likely to require mechanical ventilation (OR 1.58, 95% CI 1.02 – 2.44, p =0.04), ICU admission (OR 1.58, 95% CI 1.09 – 2.29, p =0.02), longer hospital LOS (RR 1.30, 95% CI 1.09 – 1.55, p<0.003), and have higher mortality (HR 1.53, 95% CI 1.01– 2.33, p=0.04) compared to the non-asthma cohort. Inhaled corticosteroid use and eosinophilic phenotype was not associated with significant differences. Interestingly, moderate asthma patients had worse outcomes while severe asthma patients did not.

Conclusion

Asthma was associated with severe COVID-19 after controlling for other factors.

INTRODUCTION

SARS-CoV-2 is the novel coronavirus responsible for coronavirus disease 2019 (COVID-19), a global pandemic that has to date affected 418 million people worldwide, with over 78 million total cases in the United States as of February 2022[1]. The Centers for Disease Control and Prevention (CDC) identified patients with several comorbidities, including chronic lung diseases like chronic obstructive pulmonary disease (COPD) and asthma, as high risk for severe COVID-

19[2]. Epidemiological studies have elucidated several risk factors for severe illness, including age, diabetes, obesity, hypertension, pulmonary disease, and immunosuppression[3]. Chronic lung disease is a risk factor for illness severity in COVID-19, including need for hospitalization, ICU admission, and mortality[4]. However, there have been conflicting reports on the role of asthma as a risk factor for more severe disease, with published studies showing lower mortality between asthma and non-asthma cohorts[5], no difference[6, 7], or increased mortality[8]. The current literature is challenging to interpret given a lack of uniform definitions of asthma outcomes and large variability of comorbidities accounted for in statistical analyses.

Over the past year, management of COVID-19 in hospitalized patients has changed substantially as data regarding use of therapeutics have evolved with ongoing research. With initial uncertainty regarding the use of corticosteroids early in the pandemic, many published guidelines discouraged the use of corticosteroids for treatment of SARS-CoV-2 alone[9] until results from the RECOVERY trial showed dexamethasone use resulted in mortality benefits for those receiving supplemental oxygen and mechanical ventilation in July 2020[10]. Corticosteroids are a cornerstone of therapy in treatment of acute asthma exacerbations, the majority of which are viral mediated.[11] It is unclear if the evolution of COVID-19 care as the pandemic progressed has resulted in differential outcomes for asthma patients.

The primary aim of this study was to evaluate the impact of asthma on COVID-19 related outcomes in a cohort of hospitalized patients at a tertiary academic center. The secondary objective was to determine how COVID-19 related outcomes have changed over the past year, specifically focused on the cohorts before and after dexamethasone became widely accepted as being beneficial in hospitalized patients with COVID. We hypothesize that asthma will be associated with an increased risk of poor outcomes in patients hospitalized with COVID-19,

however we anticipate that this increased risk will not be evenly distributed and that some asthma phenotypes may be more at risk than others.

METHODS

Identification of patients with asthma and COVID-19

This retrospective study was conducted at a single academic institution using databases derived from the electronic health record. COVID-19 patients were identified using the ICD-10 code for COVID-19 with confirmatory PCR testing at our institution or done at an outside institution, a positive PCR test during the admission, or a previous positive PCR test twenty-one days prior to or fourteen days after the admission. Patients admitted between March 4th – December 31st, 2020 were included. This cohort included patients that were not vaccinated against COVID-19 as vaccines were not widely available at that time. The presence of asthma was identified using ICD-10 code of J45.xx before, during, or after the encounter, which yielded 140 encounters in the first group (March – June 14th) and 127 encounters in the second group (June 15th – December). Patients were divided based on months of the year in 2020 as treatments for COVID-19 rapidly changed in the latter part of the year and this was a potential confounder. Verification of asthma diagnosis was performed by clinicians using chart review. Patients with an incorrect history of asthma (n=12) were reassigned to the non-asthma cohort. Exclusion criteria included pediatric patients (n=55). For patients with multiple encounters (n=30), the first encounter was selected. Manual chart abstraction was performed on the remaining encounters to confirm asthma status using clinician diagnosis of asthma with prescribed medications for asthma. This yielded a final asthma cohort of 183 patients, 110 patients in group 1 and 73 patients in group 2. Our non-asthma cohort consisted of 1319 adult patients (age>18) that met our definition of COVID-19 positivity as above without a diagnosis of asthma (Figure 1).

Identification of asthma severity and phenotype

For each patient with asthma, asthma specific variables including maintenance medications and pulmonary function testing (PFTs) were abstracted following manual chart review. Asthma severity was classified based on home medications using Global Initiative for Asthma strategy 2020 classification (GINA steps 1-5)[12]. Analyses compared GINA steps 1 and 2 (mild) vs. step 3 (moderate) vs. steps 4 and 5 (severe). Asthma phenotype (eosinophilic vs non eosinophilic) was also identified using highest absolute eosinophil count (AEC) in the preceding 24 months (greater than or equal to 0.3 K/μL considered eosinophilic asthma) and highest IgE level (kU/L) was noted. Severity was also compared by inhaled corticosteroid use (taking ICS vs. not taking ICS).

Outcomes

Outcomes included (1) death, (2) ICU admission, (3) mechanical ventilation, (4) total hospital length of stay and (5) ICU length of stay.

Identification of clinical characteristics and comorbidities

We identified the initial laboratory measurements for each patient including white blood cell count, absolute eosinophil counts, absolute lymphocyte counts, ferritin, D-dimer, and c-reactive protein (CRP). We utilized systematized nomenclature of medicine – clinical terms (SNOMED-CT) technology to identify concepts that matched our comorbidities of interest including obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), hypertension, coronary artery disease (CAD), diabetes and obesity (based on a BMI > 30) in both asthma and non-asthma cohorts. Charlson comorbidity index was used to assess global comorbidity burden[13]. Smoking status was also assessed and classified as current, former, never smoker or unknown smoking status. We identified whether patients were transferred in from on outside facility to account for potential selection bias given the likelihood that these patients were transferred due to more severe illness that required a tertiary care center.

Statistical analysis

Descriptive characteristics of asthma vs. non-asthma were provided using medians and interquartile ranges for continuous characteristics and frequencies and percentages for categorical characteristics. Descriptions were also provided among asthma patients by GINA step, eosinophilic asthma, and inhaled corticosteroid (ICS) use. Survival was analyzed using Cox-proportional hazards models. The binary ICU admission and mechanical ventilation outcomes were modeled using logistic regression. Total hospital and ICU length of stay in days modeled using negative bionomial regression with a log-link function. Separate models were fit for each asthma variable (i.e., asthma vs. no asthma; GINA step; eosinophilic asthma; ICS use). All models were adjusted for age, sex, race, ethnicity, transfer status, smoking status, time of illness in the pandemic (group 1 vs 2), OSA, COPD, hypertension, CAD, diabetes, obesity, and CCI. These potential confounders were selected a priori based on the literature and plausibility.

Unadjusted models for each of these variables are also reported. Analyses were performed in SAS V9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Comparison of baseline demographics, comorbidities and outcomes in asthma and non-asthma patients with COVID-19

The median age of asthma patients was significantly lower (56 years, p<0.001) vs. non-asthma patients (62 years) (Table 1). There was also a significant difference in gender representation with more asthma patients (65%) being female than non-asthma patients (41%, p<.001). There was no difference in race across both cohorts. The number of outside hospital transfers were also similar between cohorts, accounting for 20% of the asthma cohort and 20% of the non-asthma cohort (Table 1). The prevalence of asthma in our cohort was 12.2%, consistent with the reported asthma prevalence between 7.4% - 17% in nationwide cohorts[14, 15] as well as the asthma prevalence statewide[16].

COVID-19 positive patients with asthma were more likely to have OSA (32% as compared to 15%, p<0.001) and to be obese (64% versus 48%, p<0.001, Table 1) than non-asthmatics. There was no significant difference between the prevalence of COPD, HTN, CAD, and diabetes between the two groups. The Charlson Comorbidity Index was significantly higher in the asthma patients with a median of 3.0 compared to 2.0 in non-asthma patients (p=0.002, Table 1). There was no difference in smoking status between the asthma and non-asthma cohorts.

Baseline laboratory data of COVID-19 patients based on asthma status

When comparing baseline laboratory values across patient groups, we found no difference between the asthma and non-asthma cohorts in the median absolute lymphocyte count, C-reactive protein, or D-dimer; however, asthma patients had significantly lower mean ferritin

levels (499.3 [192.2 -1089.4] vs 691.8 [303.5-1366.1] mg/L) as compared to those without asthma (Table 1). There was no difference between eosinophilic asthma vs non-eosinophilic asthma patients in baseline laboratory values, however when stratified by GINA step, moderate asthma (GINA 3) patients had higher CRP and ferritin compared to mild (GINA 1-2) or severe asthma (GINA 4-5): median CRP 7.7 vs. 15.2 vs. 6.0; median ferritin 509.9 vs. 683.9 vs. 330.9 for mild, moderate, and severe respectively (Table 2).

Stratification of asthma severity by GINA step, eosinophilia and inhaled corticosteroid use

Among COVID-19 positive patients with asthma, there were 104 patients with mild asthma (GINA step 1 and 2), 29 patients with moderate asthma (GINA step 3), and 49 patients with severe asthma (GINA step 4 and 5, Table 2). When stratified by highest historical AEC count, 33% of patients were characterized as eosinophilic asthma phenotype and 58% had non-eosinophilic asthma (Table 2). The median eosinophil count was 200 cells/µl and the median IgE level was 177.5 kU/L, but prior IgE level was missing on 163 asthma patients therefore we did not perform further analyses utilizing this variable. There were 16 patients without asthma phenotype determination given lack of AEC prior to index hospitalization (Table 2).

In terms of maintenance medications among patients with asthma, 48% of patients were on inhaled corticosteroids (ICS), 36% on long-acting beta agonists (LABA), 10% on long-acting anti-muscarinic antagonists (LAMA), 21% on leukotriene receptor antagonists (LTRA), 4% on maintenance oral corticosteroids (OCS), and 3% on biologics. Pre-COVID pulmonary function tests were available on a third of the cohort and the median FEV1% was 76%, median FEV1/FVC ratio 74%, and FEF25-75% 49% (Table 2). Compared by GINA step, patients with mild asthma were younger than those with moderate or severe asthma, more likely to be transferred from an outside facility, and less likely to have an eosinophilic phenotype (Table 2). There were no significant differences in race, ethnicity across GINA steps. In terms of

comorbidity burden, moderate and severe asthma patients had a median CCI score of 3 and 4 respectively which is higher than mild asthma patients (CCI 2, p=0.04). Patients with GINA 4-5 asthma were more likely to have OSA, COPD and hypertension compared to GINA 1-3 patients (p=0.004, p=0.001 and p=0.03 respectively, Table 2).

Outcomes of COVID-19 based on asthma status

With a primary endpoint of survival probability, the unadjusted model did not show a significant difference in survival between patients with and without asthma (Figure 2). Additionally, there were no unadjusted differences in the other COVID-19 related outcomes of interest. However, in adjusted models, that accounted for age, gender, ethnicity, smoking status, timing of illness in the pandemic, transfer status, comorbidities, and CCI score show a statistically significant association between asthma and worse outcomes such as death, mechanical ventilation, ICU admission and hospital LOS (Figure 3). Using multivariable regression models, the hazard ratio for death was 1.53 (95% CI 1.01– 2.33, p=0.04) for asthma patients (Figure 3). Overall, asthma patients also had higher risk for mechanical ventilation (OR 1.58, 95% CI 1.02 – 2.44, p =0.04) and ICU admission (OR 1.58, 95% CI 1.09 – 2.29, p =0.02), and longer hospital length of stay (RR 1.30, 95% CI 1.09 – 1.55, p<0.003). There were no differences in the cohorts in terms of need for renal replacement therapy or longer ICU LOS (Figure 3).

Differences in outcomes of COVID-19 patients based on GINA step, asthma phenotype, and ICS use

We assessed patients based on asthma severity and noted that moderate asthma patients had a higher odds of ICU admission (OR 2.60, 95% CI 1.03-6.54, p=0.04), longer hospital LOS (RR 2.01, 95% CI 1.29 – 3.14, p<0.002), and ICU LOS (RR 2.02, 95% CI 1.03-3.95, p<0.002), compared to mild asthma patients, although this effect was not observed with severe asthma patients. However, it is worth noting that as the sample size for the moderate group is smaller

this could result in larger confidence intervals making the significance of this finding less certain. Severe asthma patients had shorter hospital length of stay (RR 0.80, 95% CI 0.65 – 1.00 p<0.04). There were no differences between groups in terms of hazard ratio of time to death, need for mechanical ventilation, or need for dialysis (Figure 4, eTables 1-6).

Grouping asthma patients with COVID-19, by eosinophilic vs. non-eosinophilic asthma there were no differences between the two groups in terms of mechanical ventilation, ICU admission, need for dialysis, hospital or ICU LOS. ICS use did not have a favorable impact on hospital LOS, ICU LOS, death rate, ICU admission, need for mechanical ventilation, or dialysis (Figure 4, eTables 1-6).

Differences in outcomes of asthma patients with COVID-19 based on timing of illness

When further stratified by timing of illness in the pandemic (group 2 vs group 1), those admitted in the second half of the year had substantially improved outcomes compared to those in group 1, including need for ICU admission (OR 0.38, 95% CI 0.2 – 0.9, p=0.02) and need for mechanical ventilation (OR 0.28, 95% CI 0.10 – 0.76, p=0.01), hospital LOS (RR 0.54, 95% CI 0.50 – 0.57, p<0.001), and ICU LOS (RR 0.84, 95% CI 0.77-0.92, p<0.001). There were no differences between the two groups in terms of hazard ratio of death or need for dialysis. Dexamethasone use was considered for both groups given the impact of this treatment on COVID related outcomes. Patients in group 1 rarely received dexamethasone and its use did not differ between asthma and non-asthma patients (2% of asthma vs 3% of non-asthma patients, p=0.48). However, in group 2 dexamethasone use was much higher with increased use in the asthma patients (55% vs 41% p=0.02).

DISCUSSION

In a single center cohort study, we examined the impact of asthma on outcomes for patients requiring admission for COVID-19 disease in the first year of the pandemic. Asthma is a disease characterized by airway hyperresponsiveness in the setting of inflammatory mediators and cytokines, which when coupled with a clinical syndrome of systemic inflammation as in COVID-19, is thought to lead to significant epithelial barrier dysfunction, pulmonary injury, and exacerbation of underlying disease [1]. Interestingly, after adjusting for risk factors our data demonstrated that asthma patients had a higher likelihood of severe COVID-19 related outcomes, including ICU admission, mechanical ventilation, longer hospital length of stay, and death though effect sizes were relatively small. There are gender disparities in asthma outcomes with female patients having a higher risk of poor outcomes from asthma, including a higher risk of asthma related mortality and thus adjusting for sex is critical[19]. Our data indicated a significant effect of female sex and older age on COVID-19 related outcomes which is the opposite of what has been found in COVID-19 infection alone where age and male sex have been shown repeatedly to be a significant risk factors for poor outcomes in COVID-19[2]. Our study highlights the important finding that asthma patients are at a modestly increased risk of more severe COVID-19 disease after adjusting for known risk factors. Literature on this topic is inconsistent, some of which suggests no increased risk of severe outcomes in admitted asthma patients [2, 5, 7, 19, 20]. The inconsistencies may stem from a variety of causes such as smaller sample sizes of asthma patients from single center institutional data (n=53, n=23) or as a result of the low prevalence of asthma in the population of patients infected with COVID-19 in some countries[5, 21]. Furthermore, primary endpoints were not uniform between the studies with the utilization of a variety of outcomes including intubation[2], transfer to ICU[22], time to discharge (with pooling of discharge home or death as a singular outcome),[20] and length of stay or a combination of these outcomes as surrogates for severe COVID-19 disease. Moreover, results of univariate analysis do not consider the confounding effects of comorbidities that are

established risk factors associated with more severe disease. Our results are consistent with prior reports of prolonged duration of intubation[23] and worse clinical outcomes in large nationwide cohort studies[8, 24] . However, a meta-analysis of asthma outcomes in 57 studies, which ranged from large retrospective studies to small case series with a wide sample size range (from n=8 to n=119,528), showed non-significant higher risks of ICU admission, requiring mechanical ventilation, and death from COVID-19 in those with asthma compared to those without asthma[25].

Asthma is a heterogeneous disease with a broad spectrum of different clinical phenotypes due to distinct differences in pathophysiology. Several mechanisms have been postulated to explain how allergic asthma and T_H2 asthma can be protective in COVID-19 compared to non-allergic and/or obesity related asthma. At the cellular level, ACE2 expression is downregulated in nasal epithelial cells in the presence of allergic sensitization and inversely correlated with type 2 biomarkers[26]. As such, T_H2 high asthma and low IL-6 levels are postulated as being associated with reduced risk whereas T_H2 low asthma and high IL-6 levels are thought to be associated with increased risk[4,27]. Eosinophilic asthma is associated with allergic sensitization and T_H2 dominant inflammatory response[26] and similar mechanisms of receptor downregulation may explain the decrease in risk observed in these patients[28]. Conversely, non-allergic asthma patients demonstrate different cytokine profiles, including a predominance of T_H1 mediated neutrophil and mast cell response[29] which may help explain more severe COVID-19 outcomes in nonallergic asthma patients. In fact, an analysis using UK Biobank data showed that severe COVID-19 was driven by non-allergic asthma patients, whereas allergic asthma had no statistically significant association with severe COVID-19[24]. While eosinophilic asthma patients in our cohort (based on historical AEC >300 cells/uL) did not have significant different risk of outcomes, a recent study using a lower threshold of AEC >150 cells/uL found that pre-existing eosinophilia protects against hospital admission in asthma patients who develop COVID-19[30].

Even more interesting is their finding that development of peripheral eosinophilia while hospitalized for COVID-19 was protective against mortality[30]. This suggests that in the future the heterogeneity of asthma phenotypes must be taken into consideration when assessing risk of severe disease with COVID-19.

The impact of asthma severity on COVID-19 outcomes is also unclear. In a large UK study that utilized an approach similar to ours by stratifying asthma severity by prescribed medications prior to admission, outcomes including hazard ratio of death was worse among severe asthma patients[31]. In our cohort, moderate asthma patients had worse outcomes while severe asthma patients did not despite having a higher prevalence of co-morbidities. One possible explanation for this is that a higher proportion of severe asthma patients were characterized as eosinophilic asthma phenotypes (44% compared to 25% in mild asthma) which may be a contributing factor. We postulate that the severe asthma cohort was receiving more intensive asthma treatment that may have contributed to improvements in COVID related outcomes. This cohort was receiving biologics and higher doses of inhaled corticosteroids ICS that would have resulted in decreased baseline inflammation and this may have had protective effects. Given the small sample size of our moderate (n=29) and severe (n= 49) asthma patients, more research is needed to fully elucidate the impact of asthma severity and baseline treatment on COVID-19 outcomes. ICS use has been thought to cause a reduction in ACE2 in a dose response manner[4, 32], and previous studies have shown that ICS use was not associated with increased risk of hospitalization or mortality due to COVID-19[33]. ICS use was not associated with longer length of stay in our cohort and did not change outcomes or mortality. Patients with asthma should be encouraged to adhere to ICS based therapies[33-35].

Our study has potential limitations, including a single center cohort, however our health system is a referral center for tertiary care and thus we received a large number of transfers from

hospitals around the state of Michigan which resulted in enrichment of the cohort with more socially and racially diverse populations. Patients were transferred at different points in their course of illness however there was equal representation of these patients in the asthma and non-asthma cohorts. Furthermore, we adjusted for transfer status in each multivariate model, which also accounts for level of care at presentation since most patients arrived mechanically ventilated. Another key limitation is the missing data needed to accurately phenotype our asthma cohort. Prior quantitative IgE and fraction of exhaled nitric oxide levels were missing on most of the cohort of asthma patients which precluded our ability to fully characterize asthma endotypes. In addition, many asthma patients were missing lung function measurements prior to admission and therefore baseline lung function impairments and the impact of lung function on COVID-19 related outcomes could not be determined in our cohort. We also were not able to address the impact of poor asthma control on outcomes for hospitalized patients with COVID-19. Future studies looking at the impact of poor asthma control including ACT scores, symptom control, and exacerbation frequency will be important to address this question. Our study focused on the outcomes of asthma patients already hospitalized with COVID-19, leaving unanswered questions about whether asthma is a risk factor for acquiring COVID-19 in the community and if these patients are more likely to be hospitalized then the general population. While our data proves useful for prognostication for hospitalized patients, many patients with COVID-19 are not admitted to the hospital and selecting only hospitalized patient can induce bias exaggerating the effect of risk factors on poor outcomes like ICU admission or death.

The finding that outcomes from COVID-19 improved over the course of the year are indicative of advances in our knowledge regarding the disease and improvements in care. The improvement in these outcomes likely reflects improvements in COVID treatments over time. For example, dexamethasone was used more often in group 2 than group 1 (42% vs. 3% $p<0.01$). Our data indicate that asthma patients were more likely to receive dexamethasone in the hospital despite

the fact that COVID-19 is known to cause parenchymal disease and generally does not cause asthma exacerbations[36]. Use of systemic corticosteroids is common in the management of hospitalized asthma patients and thus the use of dexamethasone may be more liberal in this population and not follow the strict recommendations guiding the use of dexamethasone for COVID-19 pneumonia.

Our study demonstrates the importance of accounting for sex, age and disease heterogeneity when determining the impact of COVID-19 on asthma outcomes. The lack of consensus on this topic would be resolved by harmonization of definitions of disease characteristics and outcomes. In general, the data that is available indicates that currently available asthma therapies do not result in negative consequences in the presence of COVID-19 infection and therefore patients should be reassured that adhering with asthma therapies is the most appropriate course of action at this time. Further research is required to parse out the specific asthma features that are associated with increased risk and our data suggest that it is premature to conclude that asthma is not associated with an increased risk of poor outcomes with COVID-19.

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Figure 1. Flowchart depicting patient selection for asthma and non-asthma cohorts

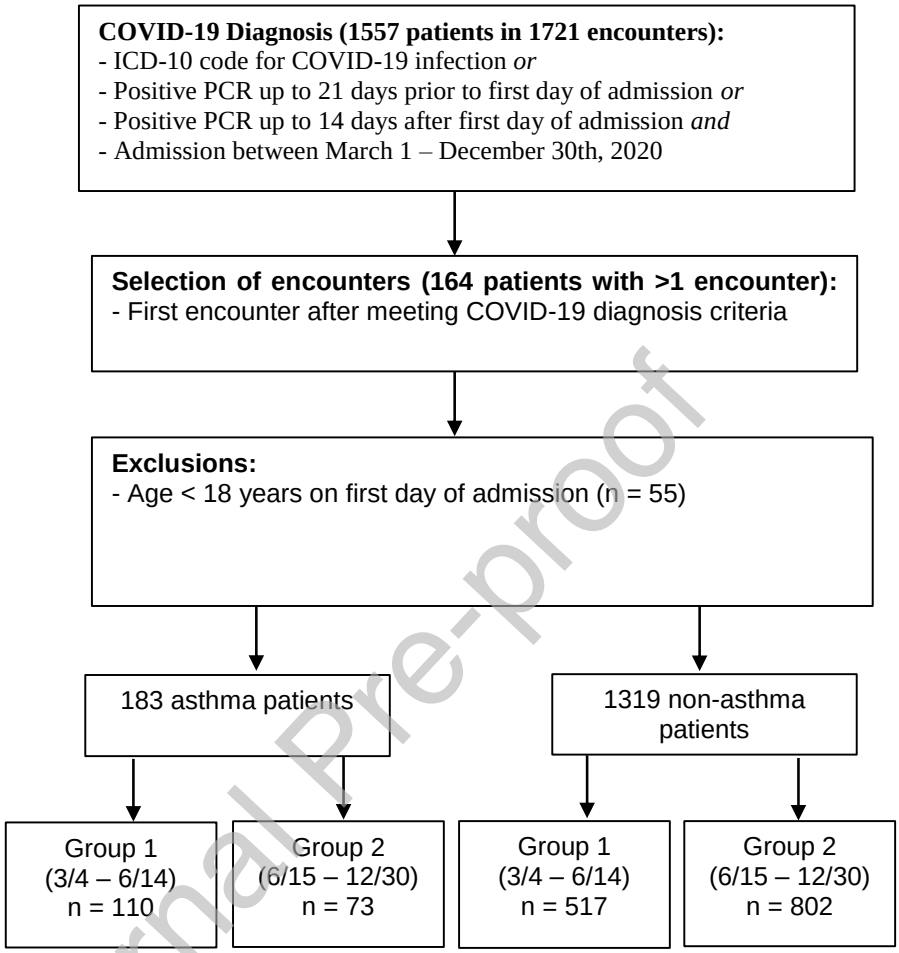

Figure 2. Survival by asthma status

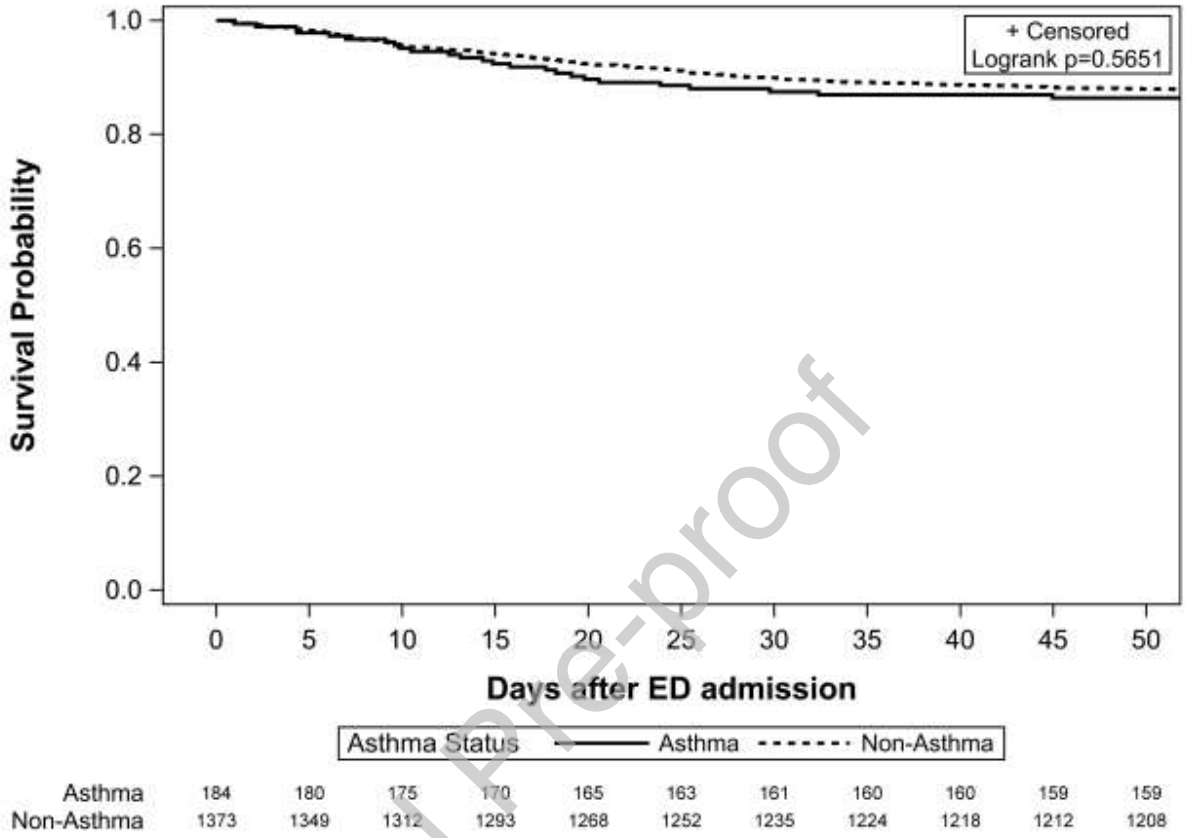

Figure 3. Impact of asthma on outcomes. All models adjusted for age, sex, race, ethnicity, transfer status, OSA, COPD, hypertension, CAD, diabetes obesity, CCI, and smoking status. Cox proportional hazards models used for death; logistic regression used for ICU admission, mechanimal venilation, and dialysis; negative binomial regression used for ICU and hospital length of stay.

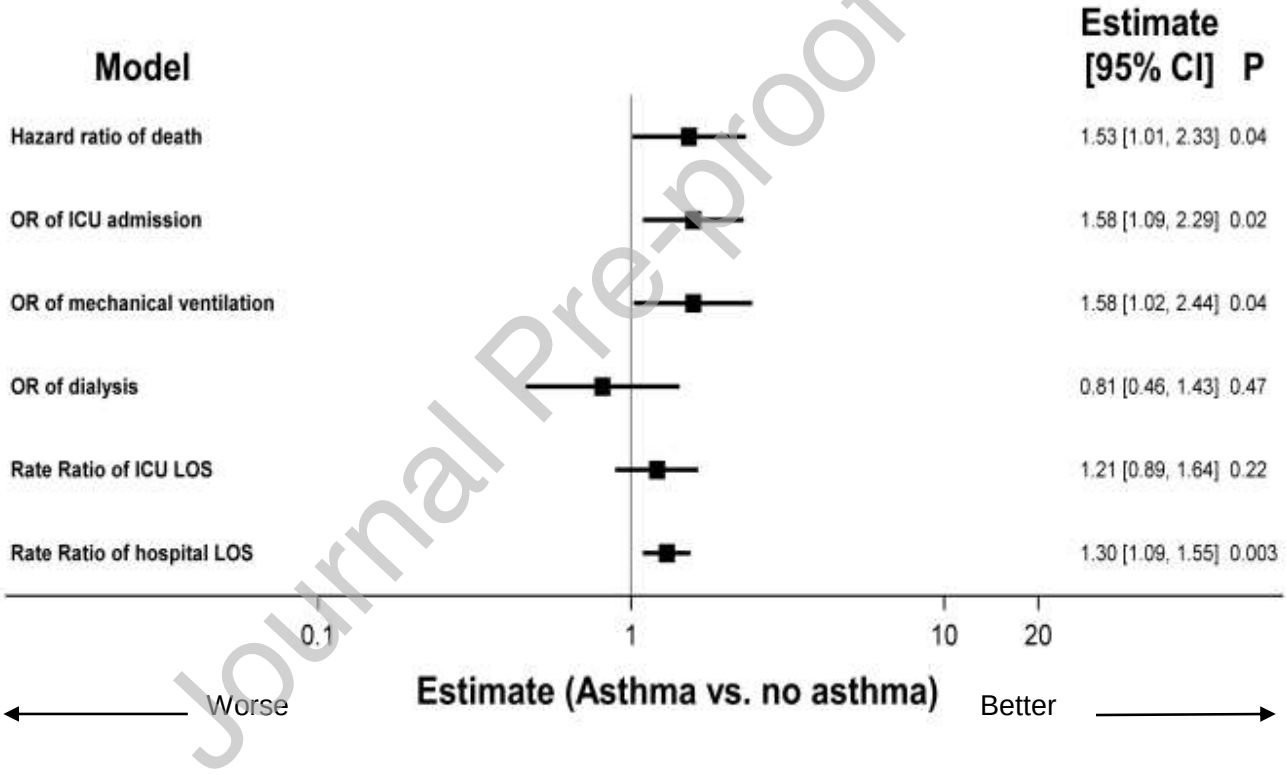

Figure 4. Impact of GINA step, asthma phenotype and ICS use on outcomes. All models adjusted for age, sex, race, ethnicity, transfer status, OSA, COPD, hypertension, CAD, diabetes obesity, CCI, and smoking status. Cox proportional hazards models used for death; logistic regression used for ICU admission, mechanimal venilation, and dialysis; negative binomial regression used for ICU and hospital

length of stay.

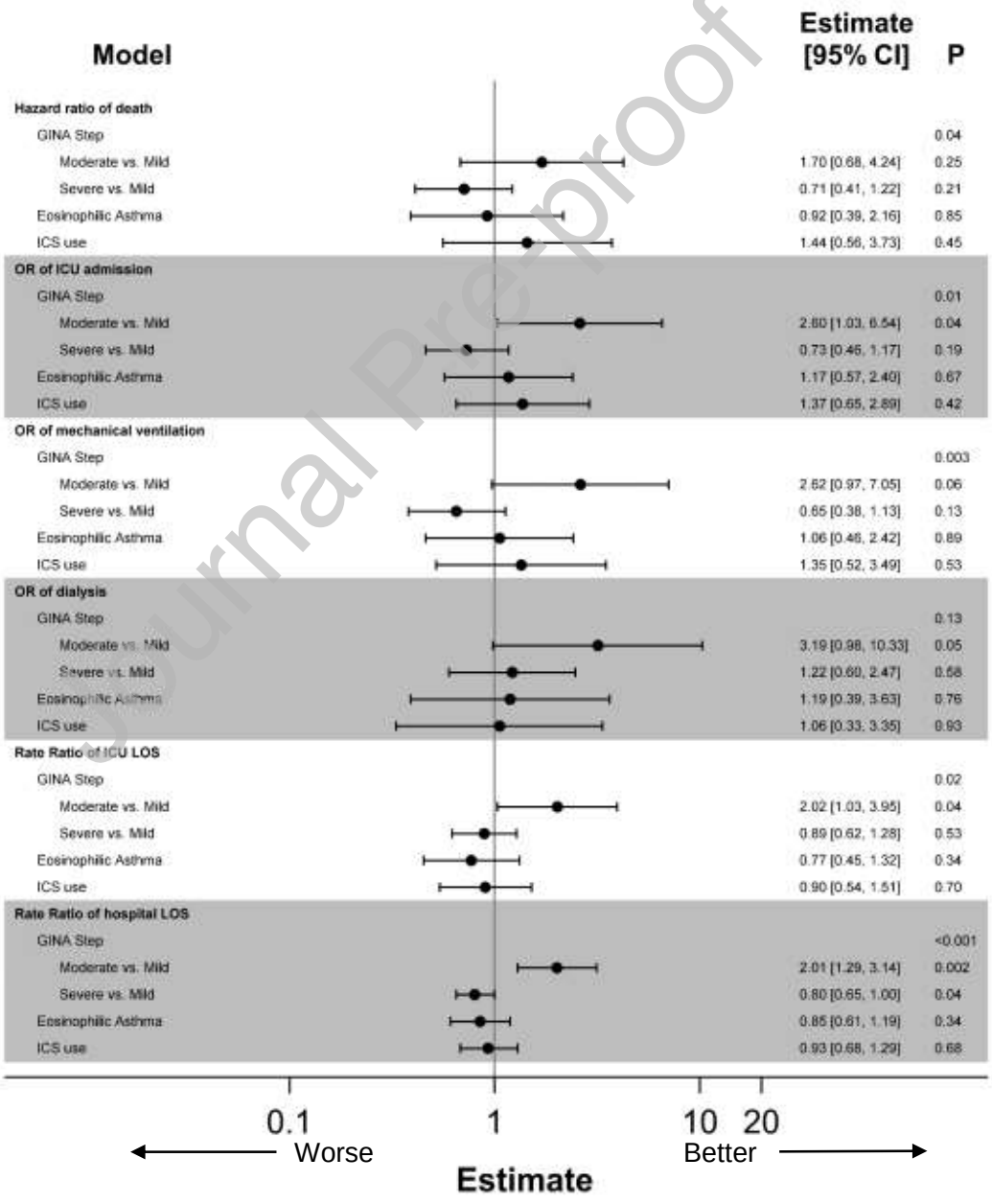

Table 1. Clinical characteristics of patients with and without asthma

Characteristic	Asthma (N=183)	Non-Asthma (N=1319)	*P*[a]
Demographics			
Age (years), median (IQR)	56 (43.0 - 66.0)	62.0 (49.0 - 72.0)	**<0.001**
Female, N (%)	119 (65)	547 (41)	**<0.001**
Race, N (%)			0.18
American Indian/Alaska Native	0 (0)	6 (0)	
Asian	4 (2)	46 (3)	
Black	63 (34)	327 (25)	
Native Hawaiian/other pacific islander	0 (0)	1 (0)	
White	100 (55)	810 (61)	
Other	8 (4)	67 (5)	
Unknown	8 (4)	62 (5)	
Hispanic	6 (3)	41 (3)	0.90
Outside hospital transfers, N (%)	37 (20)	270 (20)	0.94
Admit Group, N (%)			**<0.001**
1 (March 4 – June 14th)	110 (60)	518 (39)	
2 (June 15 – December 31)	73 (40)	801 (61)	
Comorbid Conditions			
Charlson Comorbidity Index, median (IQR)	3.0 (1.0 – 5.0)	2.0 (0.0 – 5.0)	**0.002**
Comorbid diseases, N (%)			
OSA	59 (32)	200 (15)	**<0.001**
COPD	12 (7)	104 (8)	0.53
Hypertension	86 (47)	578 (44)	0.42
CAD	23 (13)	175 (13)	0.79
Diabetes	55 (30)	382 (29)	0.76
Obesity	118 (64)	631 (48)	**<0.001**
Smoking status, n(%)			0.72
Current	4 (2)	46 (3)	
Former	52 (28)	402 (30)	
Never	89 (49)	605 (46)	
Unknown	38 (21)	266 (20)	
Laboratory values at presentation			
White blood cell count (cells/µL, median (IQR)	7.2 (5.0 – 10.3)	7.1 (5.1 - 10.1)	0.95
Ferritin (mg/L), median (IQR)	499.3 (192.2 - 1089.4)	691.8 (303.5 – 1366.1)	**0.001**
D-dimer (mcg/ml), median (IQR)	1.0 (0.6 – 2.6)	1.1 (0.6 - 2.1)	0.92
C-reactive protein (mg/L), median (IQR)	8.0 (4.0 – 14.7)	7.7(3.8 – 15.7)	0.98
Absolute lymphocyte count (cells/µL), median (IQR)	1.0 (0.6 - 1.3)	0.9 (0.6 - 1.3)	0.78

IQR = interquartile range

[a]p value represents Fisher exact test for categorical variables

[b]Missing data from asthma cohort included 15 without ferritin, 22 without D-dimer, 17 without CRP, 5 without ALC

Missing data from non-asthma cohort included 332 without ferritin, 363 without D-dimer, 357 without CRP, and 69 without ALC count

Table 2. Clinical characteristics of asthma cohort, stratified by GINA step therapy

		GINA step therapy			
Characteristic	Asthma (N=183)	Mild asthma (GINA steps 1 & 2) (N=104)	Moderate asthma (GINA step 3) (N=29)	Severe asthma (GINA steps 4 & 5) (N=49)	P
Age (years), median (IQR)	56 (43.0 - 66.0)	53.0 (39.5 - 64.0)	63.0 (54.0 - 67.0)	59.0 (53.0 - 67.0)	**0.03**
Female, N (%)	119 (65)	67 (64)	20 (69)	32 (65)	0.90
Race, N (%)					0.45
American Indian/Alaska Native	0 (0)	0 (0)	0 (0)	0 (0)	
Asian	4 (2)	2 (2)	2 (7)	0 (0)	
Black	63 (34)	37 (36)	10 (34)	15 (31)	
White	100 (55)	54 (52)	14 (48)	32 (65)	
Other	8 (4)	5 (5)	2 (7)	1 (2)	
Unknown	8 (4)	6 (6)	1 (3)	1 (2)	
Transferred from outside hospital, N(%)	37 (20)	29 (28)	4 (14)	4 (8)	**0.01**
Charlson Comorbidity Index, median (IQR)	3.0 (1.0 – 5.0)	2.0 (1.0 to 5.0)	3.0 (1.0 to 5.0)	4.0 (1.0 to 7.0)	**0.04**
Comorbid diseases**, N (%)					
OSA	59 (32)	28 (27)	6 (21)	25 (51)	**0.004**
COPD	12 (7)	2 (2)	1 (3)	9 (18)	**0.001**
Hypertension	86 (47)	43 (41)	12 (41)	31 (63)	**0.03**
CAD	23 (13)	10 (10)	4 (14)	9 (18)	0.31
Diabetes	55 (30)	28 (27)	17 (35)	17 (35)	0.53
Obesity	118 (64)	64 (62)	21 (72)	33 (67)	0.51
Laboratory values at presentation					
White blood cell count (cells/µL, median (IQR)	7.2 (5.0 – 10.3)	6.9 (4.8 –11.0)	8.8 (5.0 –10.5)	7.3 (5.3 –9.2)	0.91
Ferritin (mg/L), median (IQR)	499.3 (192.2 - 1089.4)	509.9 (213.2 – 1025.1)	683.9 (425.8 – 1472.0)	330.9 (154.6 – 762.1)	**0.04**
D-dimer (mcg/ml), median (IQR)	1.0 (0.6 – 2.6)	1.2 (0.6 –2.7)	1.4 (0.5 –3.7)	0.8 (0.5 –1.5)	0.16
C-reactive protein (mg/L), median (IQR)	8.0 (4.0 – 14.7)	7.7 (4.1 –14.5)	15.2 (7.9 –21.6)	6.0 (2.8 –9.3)	**<0.001**
Absolute lymphocyte count (cells/µL), median (IQR)	1.0 (0.6 - 1.3)	1.0 (0.7 –1.3)	1.0 (0.7 –1.1)	1.0 (0.5 –1.4)	0.92
Eosinophilic asthma, N (%)					
Historical AEC (median (IQR))	0.2 (0.1 to 0.4)	0.2 (0.1 to 0.3)	0.2 (0.1 to 0.4)	0.3 (0.1 to 0.7)	**0.04**
Non-eosinophilic	105 (58)	66 (63)	16 (55)	23 (50)	
Eosinophilic	59 (33)	25 (24)	12 (41)	21 (46)	
Cannot be determined	16 (9)	13 (13)	1 (3)	2 (4)	
Asthma medications, N (%)					
Biologics	6 (3)	0 (0)	0 (0)	6 (13)	**<0.001**
Leukotriene antagonist	39 (21)	14 (14)	4 (14)	20 (41)	**<0.001**
Long-Acting Beta Agonist	66 (36)	3 (3)	20 (69)	43 (90)	**<0.001**
Long-Acting Muscarinic Antagonist	18 (10)	1 (1)	2 (7)	15 (31)	**<0.001**
Maintenance Oral Corticosteroids	7 (4)	2 (2)	0 (0)	4 (8)	0.07
Inhaled Corticosteroids	87 (48)	12 (12)	27 (93)	47 (96)	**<0.001**

Low dose	26 (30)	11 (85)	13 (48)	1 (2)	**<0.001**
Medium dose	44 (50)	1 (8)	14 (52)	29 (62)	**<0.001**
High dose	18 (20)	1 (8)	0 (0)	17 (36)	**<0.001**
Pulmonary function tests n=64 (18 mild asthma, 14 moderate asthma, 32 severe asthma)					
FEV1 (L), median (IQR)	2.0 (1.5 to 2.8)	2.7 (2.0 to 3.3)	1.8 (1.1 to 2.5)	1.6 (1.4 to 2.4)	0.21
FEV1 (%), median (IQR)	76.0 (53.0 to 90.0)	83.0 (78.0 to 96.0)	68.5 (43.0 to 86.0)	68.5 (54.0 to 87.0)	0.60
FEV1/FVC ratio, median (IQR)	74.0 (62.0 – 80.0)	79.5 (74.0 – 82.0)	74.0 (69.2 – 83.0)	68.0 (62.0 – 76.0)	0.80
FEF 25-75 (%), median (IQR)	49.0 (27.0 – 76.0)	69.5 (54.0 – 92.0)	43.0 (25.0 – 64.0)	40.0 (27.0 – 60.0)	0.10

Absolute eosinophil count, K/µL # Pulmonary Function Tests were available for 64 asthma patients (18 mild, 14 moderate and 32 severe). All other labs <12% missing

**Abbreviations: OSA (obstructive sleep apnea), COPD (chronic obstructive pulmonary disease), CAD (coronary artery disease) FEV1: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity; FEF: Forced expiratory flow